# Ketamine

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This chapter is vaguely related to the section of the CICM primary syllabus which lists the drugs which you're supposed to know as an intensivist. Ketamine is certainly one of those, and this is reflected in the large number of ketamine-related past paper questions:

- Question 11 from the first paper of 2022
- Question 15 from the first paper of 2019 (NMDA receptor pharmacology)
- Question 4 from the second paper of 2018 (ketamine vs. midazolam)
- Question 22 from the first paper of 2015 (ketamine vs dexmedetomidine)
- Question 16 from the second paper of 2011 (ketamine and propofol effects on $CMRO_2$)
- Question 7 from the second paper of 2010 (ketamine vs propofol)
- Question 9(p.2) from the second paper of 2007 (ketamine vs. propofol)

In summary:

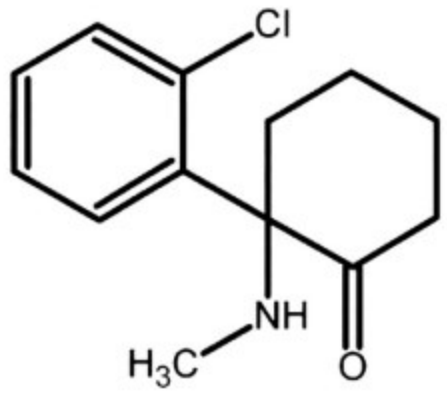
| | |
|---|---|
| **Name** | Ketamine |
| **Class** | IV anaesthetic |
| **Chemistry** | Cyclohexylamine |
| **Routes of administration** | Intravenous, intramuscular, subcutaneous, oral (rarely), buccal, transdermal and rectal |
| **Absorption** | 17% oral bioavailability |
| **Solubility** | pKa 7.5; relatively poor water solubility; 20-50% protein bound |
| **Distribution** | 1-3L/kg |
| **Target receptor** | NMDA receptor |
| **Mechanism of action** | Lodges in the pore of the NMDA cation channel, causing the receptor to become closed, and to stop binding glutamate. As a consequence, it prevents glutamate-simulated sodium and calicum influx into the cell, and potassium efflux. The result is a depressed excitatory neurotransmission |
| **Metabolism** | Metabolised by CYP450 enzymes into multiple metabolites, of which only norketamine is mildly active. |
| **Elimination** | Elimination half-life is 2.5 hrs, but redistribution (alpha) half-life is ~ 7-11 minutes |
| **Time course of action** | Onset of anaesthetic effect, following an anaesthetic dose (~2mg/kg), is within 15-30 seconds. Duration of useful anaesthesia/analgesia is about 15-30 minutes. |
| **Clinical effects** | Dissociative anaesthesia, analgesia, sialorrhoea, bronchorrhoea, bronchodilation, possible increased cerebral metabolic rate, reversal of opioid tolerance, and slightly increased skeletal muscle tone.<br><br>Haemodynamic effects are largely indirect, i.e. the result of sympathetic stimulation.<br>- Increased cardiac output<br>- Markedly increased heart rate |

| | |
|---|---|
| | - Increased mean arterial pressure initially, which rapidly renormalises<br>- Unchanged peripheral vascular resistance<br>Direct effects of ketamine on inotropy are negative. |
| Single best reference | Domino (2010) |

The examiners' preoccupation is hardly unfounded, as ketamine is an important part of the intensivists' pharmacological toolkit. Beyond that, it is a fascinating subject. Fortunately, the author's great temptation to style this *ode de ketamine* after De Quincey's *"Confessions of an English Opium Eater"* was frustrated by his lack of genuine Gonzo experiences with the substance. Others went there, but their accounts of cosmic apotheosis cannot be recommended to the CICM exam candidate, as they lack relevant pharmacokinetic details. The single best article for revision, on many levels, is Domino (2010), which represents the reflections of an original investigator who was involved in the development and testing of this drug in the 1960s. It boasts the rare combination of easy readability and dense pharmacological detail. For something a little drier, one may review the FDA PI for Ketalar or the Australian PI from Interpharma. For something utterly, unforgivingly dry, McMillan & Muthukumaraswamy (2020) explore the effects of ketamine on cerebral metabolism over 47 densely packed pages, without any regard for the cerebral metabolism of the reader.

## Chemical properties and molecular structure

Otherwise known as [2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone], ketamine is a small molecule with the formula $C_{13}H_{16}ClNO$.




It usually presents as a racemic mixture of two isomers (R- and S-ketamine), of which the S-isomer has a substantially higher anaesthetic potency. Given the

difficulty of separating stereoisomers, , nobody has ever found a commercially attractive reason to separate the R from the S, even though they have distint pharmacological effects (for instance, the R-isoform may be a better antidepressant). What you get in an ampoule is usually ketamine hydrochloride, which dissolves rather nicely in water, but which is usually offered as a saline dilution because of our cultural attachment to isotonicity.

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## Chemical Relatives

In terms of chemical lineage, ketamine belongs to a larger group of substances, usually referred to as cyclohexylamines. The synthesis of these substances was first reported by Maddox et al (1965), who discuss them in some detail. It was not the first agent of its group to be discovered. For example, its nearest chemical relative phencyclidine (PCP) was already around in the late 1950s, and was initially known as Sernyl or Sernylan when Parke Davis & Company tried to sell it to psychiatrists (Luby et al, 1959). Hilariously, it was instantly unpopular among psychiatrists because it produced *"intensification of the thought disorder"* and made the already psychotic patients *"assertive, hostile, and unmanageable"*; so much so that the company based its marking strategy on offering the drug as a research model of schizophrenia. These qualities, as well as its long duration of action, made for some interesting post-operative phenomena, when it was first used in humans as an anaesthetic.

However, PCP did have some highly desirable anaesthetic effects. After a 10mg/kg injection, monkeys could tolerate abdominal surgery with no additional anaesthetic. *"During the operation the animal had its eyes open and looked about unconcernedly"*, wrote Greifenstein in 1958. The same authors reported their human trials as highly positive, except that the surgeons complained of the patient's *"garrulousness"* intraoperatively, and that the patient remained delirious inappropriately sexual and/or violent for tens of hours following the procedure.

Clearly, the situation called for a shorter-acting alternative, so that the recovery room would not be filled with gibbering delirium. Parke Davis saw a commercial opportunity in this, and commissioned Calvin Lee Stevens to explore the options. They were numerous (Maddox et al list sixty options), of which eleven had biological activity as anaesthetics, and from which one (code CI-581) was finally selected for human trials. Edward F. Domino's excellent autobiographical account

of the first human experiments is definitely worth reading for some flavourful historical details (for instance, the term "dissociative anaesthetic" was coined by Domino's wife Toni, and the name *ketamine* was apparently a portmanteau of *ketone* and *amine,* though the exact etymological origin appears to be lost in deep history).

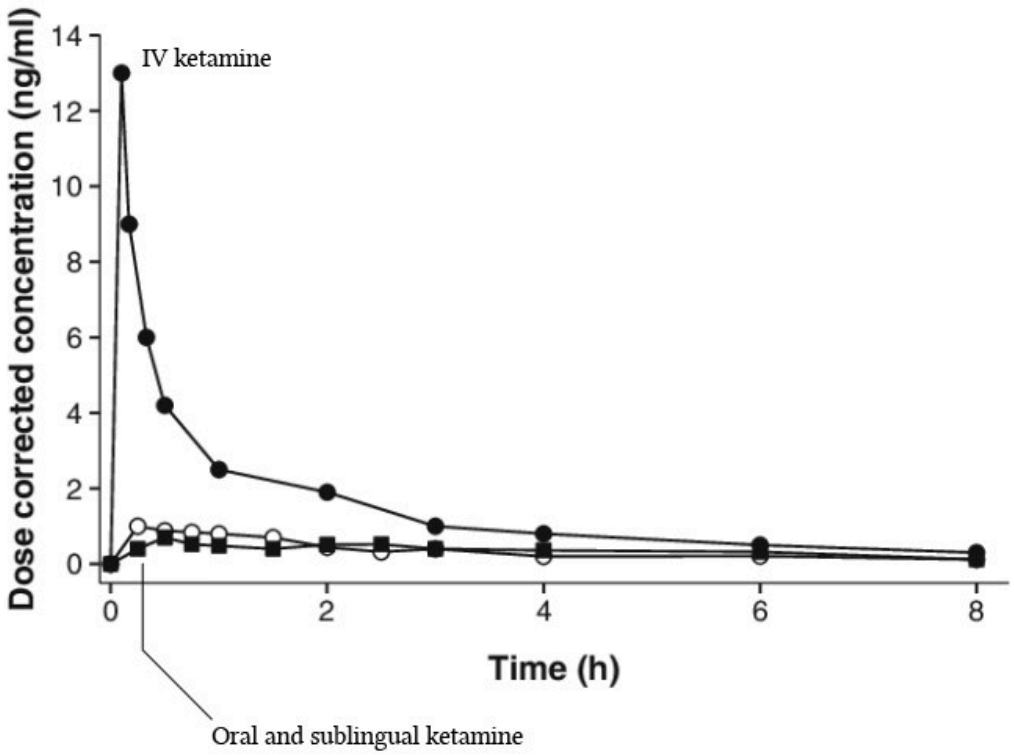
In terms of its pharmacological effects, ketamine can also be grouped with other dissociative anaesthetics. Dissociative anaesthesia is a fairly unique effect, and there aren't many substances that can claim to produce it. Apart from phencyclidine, this group also contains nitrous oxide and dextromethorphan, the over-the-counter cough syrup ingredient which remains easily available in spite of causing chronic low-grade moral panic. Additionally, minocycline has been reported to have dissociative depersonalisation effects. Antiparkinsonian drugs amantadine and memantine also bind to the same receptor as ketamine, albeit with different receptor interactions and therefore completely different effects. Among toxins, muscimol (of *Amanita muscaria*) is occasionally described as a dissociative drug, and Halpern (2004) identifies another half dozen plant-derived substances which can be loosely classed as "dissociative intoxicants", enveloped by this term largely because it is so difficult to define its boundaries.

## Administration and Absorption

Ketamine can be administered in a large number of ways. Realistically, its small molecular mass and high solubility in water and fat make it an excellent candidate for any sort of administration. The conservative intensivist will want to administer it intravenously, but prehospital protocols permit intramuscular use. It has relatively poor oral bioavailability (17%), as it is broken down by bile acids and first-pass metabolism, but some compounding pharmacies have been able to overcome this problem by creating delicious lozenges. Additionally, inhaled rectal intranasal and transdermal options also exist. Adventurous (or bored) anaesthetists have also injected it directly into the central nervous system, with only a 30% incidence of *"severe psychotomimetic side effects"*.

## Distribution

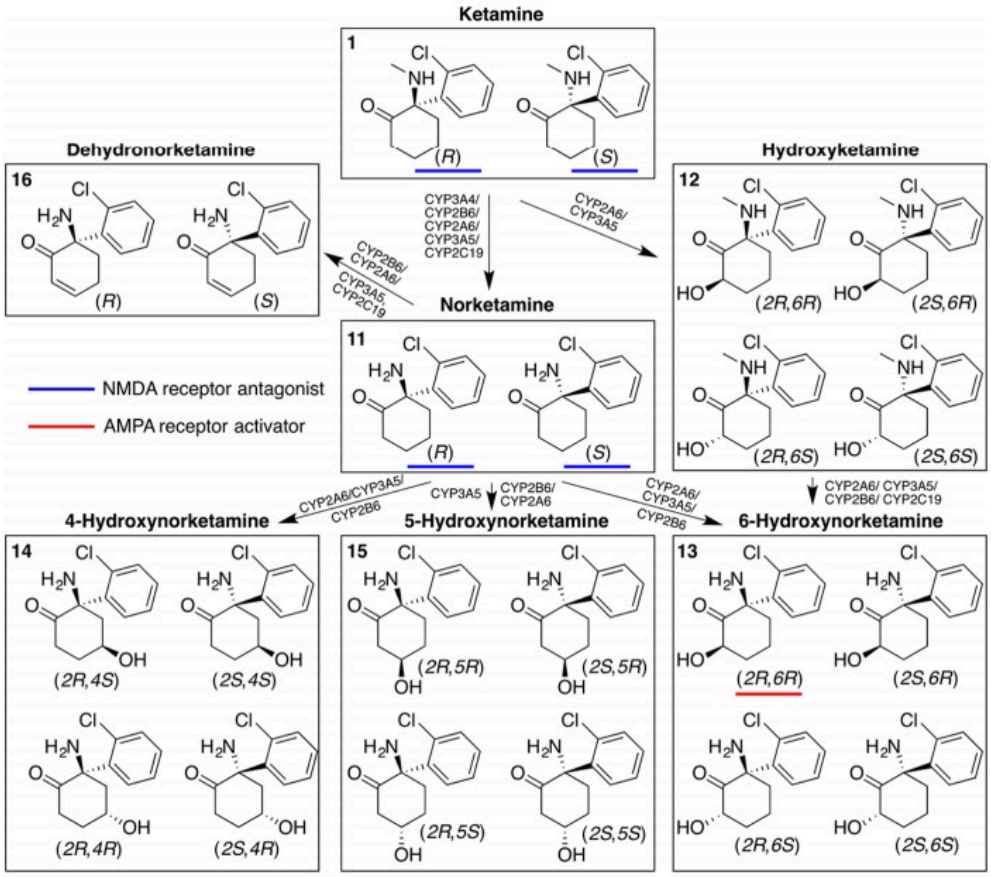
Owing to itx excellent fat solubility, ketamine is widely distributed, and has an α-half-life of only 7-11 minutes (Clements et al, 1982). Here is an excellent diagram from Peltoniemi et al (2016) which demonstrates this early rapid distribution, followed by a slow elimination phase lasting hours.




The volume of distribution is generally quoted as 1 to 3 L/kg. It is about 20-50% protein bound, mainly to albumin, and - in case anybody is interested - its pKa is 7.5.

## Metabolism and Clearance

After distributing rapidly into tissues, ketamine gradually makes its way back out into the circulation, with a β-half-life of around 2.5 hours. During this time it undergoes mainly hepatic metabolism, with multiple different metabolites, and only about 2-4% escapes unchanged into the urine. For completeness, this confusing diagram from Tyler et al (2017) is included below:




In the interests of sanity, a brief list of metabolic steps has to include:

- N-dealkylation to norketamine
- Hydroxylation of the cyclohexone ring
- Conjugation with glucuronic acid
- Dehydration of the hydroxylated metabolites to form a cyclohexene derivative

Of these, only norketamine is borderline bioactive, but not significantly so (certainly not enough to be worried after a normal dose). Keeping in mind the needs of the exam candidate, for a written answer this whole aspect should probably be summarised as "metabolised extensively by CYP450 enzymes".

## Mechanism of action and clinical effects of ketamine

Ketamine is an NMDA receptor antagonist. Specifically, it is a non-competitive antagonist of glutamate. It binds at an allosteric site which is distinct from the glutamate-binding site, but which prevents glutamate from binding to the receptor. Specifically, it is a "high-trapping" open channel blocker, so called

because when a ketamine molecule binds the open channel it causes the channel to close and becomes trapped in the pore, preventing further glutamate binding. Bolshakov et al (2003) point out that this property probably accounts for its potency as a dissociative drug, as other drugs which are less "trapped" exhibit minimal psychoactive effects. For example, memantine and amantadine also block the NMDA receptor, but with only "partial trapping", and their psychoactive properties are more subtle (merely delusional thinking and hallucinations, according to Wilcox, 2012).

Anyway, though the reader hardly needs to be reminded of it, the pharmacodynamic importance of the NMDA receptor can be described as follows:

- The NMDA receptor is a ligand-gated nonselective cation channel
- The ligands are the neurotransmitters glycine and glutamate, both of which have to bind in order to activate the receptor
- Opening of the receptor channel permits the flow of:
    - potassium (out of the cell)
    - sodium (into the cell)
    - calcium (into the cell)
- The sodium and potassium movements can depolarise the cell, i.e. the receptor can serve a synaptic function, allowing the propagation of an action potential. However, these receptors are not critically important for synaptic transmission (Blanke et al, 2008).
- The inward flow calcium is responsible for interesting intracellular second messenger effects, including neuromodulation, as well as excitotoxicity.

For the purposes of the exam, the CICM trainee should dutifully recite the NMDA blocking effects of ketamine, as this is the most important effect in terms of scoring marks. However, there are numerous other effects, described in passing by Tyler et al (2017) and Sleigh et al (2014):

- Suppression of immediate early gene expression at the site of mechanical injury
- Altered regulation of NMDA receptor1 phosphorylation
- Reduced glial fibrillary acidic protein (GFAP) expression
- Enhance brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) protein levels
- Multiple neuromodulatory effects, including:

- Enhancement of neuronal hyperpolarisation-activated cationic currents
- Increased activity of nicotinic acetylcholine ion channels
- δ and μ-opioid receptor agonism and opioid potentiation
- non-NMDA glutamate receptors
- Reduction in pontine cholinergic neuromodulation
- Increased release of dopamine and noradrenaline, both centrally and peripherally.

The clinical effects of this? They are difficult to describe. To borrow some lines from Corssen et al (1969):

> *" ...The patient appears to be "disconnected" rather than asleep... Marked horizontal and vertical nystagmus of several seconds duration preceded loss of consciousness. At this time the patient's eyes opened and remained open until the drug effect wore off. Slight to moderate increase in heart rate occurred shortly after onset of anesthesia, along with systolic and diastolic blood pressure elevations averaging 10 to 30 mm. Hg. The increase in blood pressure and heart rate lasted several minutes; the values then gradually returned to preinjection levels."*

From the inside, the experience is markedly different for the subject. Frightened travellers report ultra-realistic hallucinations, time dilation, out of body experiences, conversations with dead relatives and flashbacks to previously lived trauma. Affectionally known as "the K-hole", this state of waking nightmare tends to be observed at relatively high doses, and is usually not the endpoint pursued by a recreational user. It is unfortunate that these occasionally rather articulate individuals have so far failed to publish their adventures in critical care literature, and detailed accounts of the subjective experience are difficult to track down.

Medical professionals, whose personal exposure to ketamine is generally strictly medicinal, have attempted to describe their recollections, with occasionally awesome results. One particularly excellent account comes from Dr. Robert E. Johnston (1973), which describes the author's reaction to an epic 3mg/kg dose of IV ketamine during some sort of physiology experiment. It opens with lines from *White Rabbit,* which is still cool because this was published before they invented cliches. The author was not a veteran recreational drug user, and clearly could not find the comedy in his experience:

*"...I then became aware of my body. My right arm seemed withered and my left very long. I could not focus my eyes. Observers reported marked nystagmus. I recognised the ceiling, but thought it was covered in worms... ...Still I am afraid of it. I doubt if I ever will take it again because I fear permanent psychological damage."*

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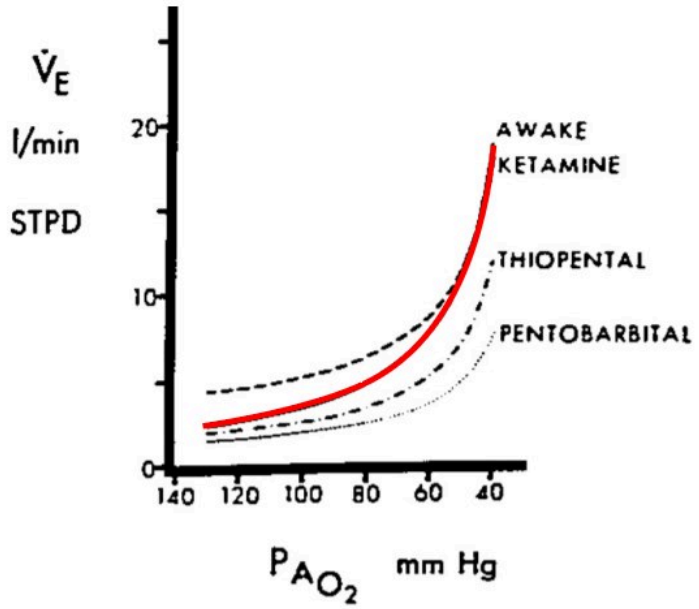
## Airway reflex and respiratory effects of ketamine

Ketamine is often touted as the anaesthetic drug which can be administered without the need to protect the airway, or fear that the patient will develop apnoea, because of the perception that it preserves upper airway and respiratory reflexes. This appears to be the case over the low dose range of ketamine, such as what one might use for some sort of periprocedural twilight sedation. In fact, Eikermann et al (2012) actually demonstrated that during a low-dose ketamine anaesthetic the airway reflexes and neck muscle tone were greater than during normal sleep.

For respiratory drive, the situation is slightly different. Ketamine truly does seem to maintain respiratory drive at low-moderate dose rates, and what is most important, it preserves the response to respiratory stimuli. To demonstrate, here is an excellent diagram from a dog study by Hirshman et al (1975), demonstrating a preserved respiratory response to hypoxia. The response, particularly in severe hypoxia, was at least as vigorous as that of awake subjects.



Beyond this effect on airway and central respiratory reflexes, ketamine also has an unexpected bronchodilator effect. It was initially thought that this was due to the blockade of calcium influx into the bronchial smooth muscle which occurs as the result of NMDA receptor blockade (NMDA receptors being expressed in the cells of the lungs and bronchi). However, it appears that ketamine-induced bronchodilation appears to occur by a mechanism which is independent of the NMDA receptor. Instead, it appears to interfere with a calcium-dependent step in histamine-induced bronchoconstriction. For example, Sato et al (1998) were unable to reduce the ketamine-induced relaxation by exposing smooth muscle to NMDA *agonists*, which suggests NMDA receptors play no role in the mechanism. Irrespective of how it works, ketamine is generally listed alongside "proper" bronchodilators in the list of drugs used to manage status asthmaticus (eg. in reviews like Goyal & Agrawal, 2013).

## Haemodynamic effects of ketamine

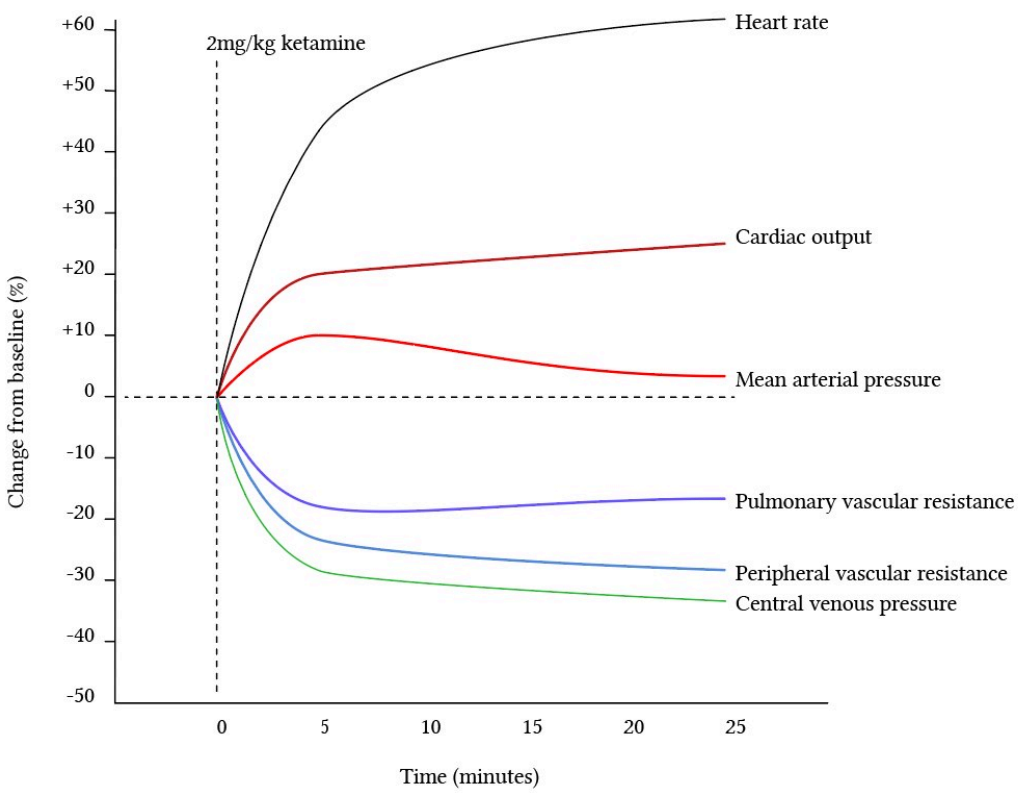
As a part of its reputation as an "extreme" anaesthetic, ketamine is generally described as a haemodynamically neutral drug, which does not have any adverse cardiovascular effects and which is therefore suitable for patients in advanced stages of shock. The specific elements of what ketamine does to the haemodynamic variables, however, is somewhat less clear. Most of the recommended textbooks for ANZCA or CICM exams do not specifically describe the effects of ketamine on different variables within the circulatory system, and where they do, the reported effects are occasionally contradictory. Here's a table of the usual suspects and their takes:

Textbooks, and How They Differ in their Description of the Haemodynamic Effects of Ketamine

| | CO | MAP | PAP | SVR | PVR | CVP |
|---|---|---|---|---|---|---|
| Scarth (2016) | Increase | Increase | - | - | - | Increase |
| Katsung (2020) | Increase | Increase | - | - | - | - |
| Stoelting (2022) | Increase | Increase | Increase | Decrease | Increase | Increase |
| Evers (2011) | Increase | Increase | - | Increase | - | - |
| Millers (2019) | Increase | Increase | Increase | Increase | Increase | - |
| Goodman & Gilman | Increase | Increase | - | Decrease* | - | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| Peck & Hill (2007) | Increase | Increase | - | - | - | - |
| Rang & Dale (2012) | Increase | Increase | - | - | - | - |
| Schüttler (2008) | Increase | Increase | - | Decrease | Decrease | |

Though one's self-preservation instincts demand that these effects be memorised and reproduced in exam answers, it is hard to know where these data came from, or which to believe. This is disturbing especially in the context of published experimental data, which is often contradictory. One of the most commonly quoted studies that describe the haemodynamic effects of ketamine appears to be Folts et al (1975) who gave 2mg/kg of ketamine to twenty mongrel dogs and measured every conceivable cardiovascular parameter. The authors chose to report their data in a series of messy graphs, using nonstandard abbreviation (for example, their $CMRO_2$ refers to *cardiac* metabolism of oxygen). These data had to be concatenated and modernised for human consumption:




In normal words, the haemodynamic effects of ketamine from this study were:

- Decreased pulmonary vascular resistance
- Decreased peripheral vascular resistance
- Decreased central venous pressure

How to reconcile this with what the CICM trainee will see in textbooks? Possibly, direct peripheral and indirect central sympathomimetic effects may be antagonistic.

Goodman & Gilman report that ketamine is directly a vasodilator, but that indirect sympathomimetic effects usually overwhelm this, which means it can act as either an inodilator or an inoconstrictor. The latter appears to be the consequence of direct sympathetic effects: ketamine enhances the release of synaptic catecholamines in the CNS as well as peripherally. Doak et al (1993) were able to demonstrate this by blocking (some of) the haemodynamic effects of ketamine by using clonidine. Some effects persisted, probably because the clonidine had no effect on the increases in peripheral catecholamine release. The mechanism of exactly *how* this happens remains unclear. Kubota et al (1999) pursued this subject in rats and were unable to reach a conclusion (other than to confirm that it happens), suggesting only that *"it might indirectly activate noradrenergic neurons... via other neurotransmission systems"*. Taken in isolation, ketamine is actually a negative inotrope: its direct effects on the cardiac myocytes is to reduce intracellular calcium availability and to decrease contractility (Kongsayreepong et al, 1993).

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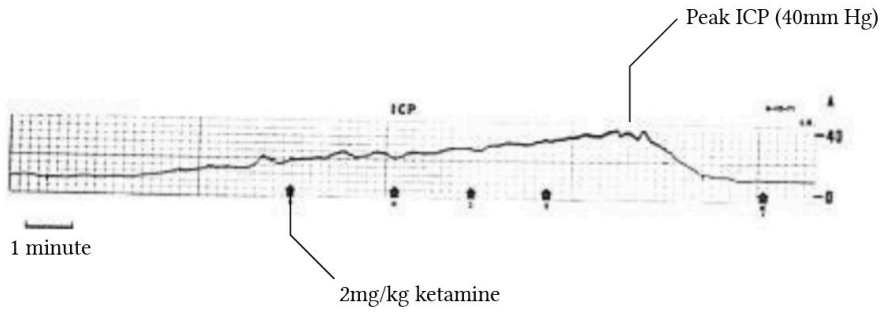
## Effect of ketamine on the cerebral metabolic rate and ICP

All the sophisticated modulatory effects are responsible for multiple applications of ketamine (eg. for chronic pain, or as an antidepressant) are of course of no interest to the early-stage CICM trainee who will most likely be interested mainly in the anaesthetic properties of this drug. Or, more directly, in the effects of ketamine on the cerebral metabolic rate and $CMRO_2$, which has been the topic of several CICM part paper questions. The college examiners seem to think that it increases the cerebral metabolic rate, which means the trainees are also expected to express this opinion in order to pass the exam, but in reality, the situation may be slightly different.

The impression that ketamine absolutely definitely increases the cerebral metabolic rate comes from the early 1970s, when researchers were enthusiastically exploring the potential of a novel anaesthetic. Initially, there was no hint of any anti-ketamine bias in the neuroanaesthetic literature. Brown et al (1970), describing their experience with this agent in the Royal

Children's Hospital in Melbourne, reported four neurosurgical procedures with a ketamine anaesthetic, with no mention of any adverse effects, or any concern from the anaesthetist that such effects might arise. This quickly changed when people started reporting intraoperative increases in ICP associated with its use. Supported by several letters to the editor of Lancet, Wyte et al (1972) produced two case reports and a discussion which seemed to suggest that ketamine causes an acute rise in ICP. The original pressure tracings are reproduced below with annotations. To be sure, this was not much of a scientific signal (two patients with hydrocephalus, paediatric population), but an ICP increase up to 40 mmHg was nothing to scoff at, and it produced a sense of dread in the investigators. *"The use of ketamine anesthesia for patients with neurologic lesions should be limited to those cases in which there are no signs and symptoms of increased intracranial pressure"*, they fearfully concluded.




On the basis of this and other similar publications, ketamine use was banished from the neurosurgical theatres. This bias has persisted into the modern era, and is maintained by various factors, not the least of which being the ready availability of equally potent agents with none of the stigma. Why ketamine, the coroner might ask you. Why didn't you just use a barbiturate like normal people? Fortunately, some authors have fought their instinctive revulsion to publish papers in support of its use. In their 2018 piece *"Ketamine: A Neuroanesthesiologist's Friend or Foe?"*, Luthra & Rath platformed some of its benefits, including potential neuroprotective and definite anticonvulsant effects. Ketamine, they reason, possesses unique properties which make it favourable for neuroanaesthesia, not the least of which being the fact that it is a direct antagonist to the mechanism of glutamate-mediated excitotoxicity in injured neurons. The ICP changes, according to multiple points of data they present, occur mainly in patients who are breathing spontaneously, and are largely eliminated by controlled ventilation in the modern neurosurgical setting.

Of course, the attentive reader will by this stage readily point out that discussions of ICP and neuroprotection are not going to pass CICM exams, which are mainly interested in cerebral blood flow and $CMRO_2$. What actually happens there? The answer, like everything with ketamine, is complex and multifactorial.

Fortunately, we are able to rely on the analytic skills of experts, rather than ourselves trying to integrate conflicting information from numerous contradictory papers. Zeiller et al (2016) produced the most lucid and recent account of the cerebrovascular effects of ketamine in a synthesis of multiple human and animal studies. Both regional and global cerebral blood flow was increased in the majority of the reported data, by what appears to be a calcium-dependent vasodilatory mechanism. The list of limitations stretches across several pages, but the overall trend tends to favour the conclusion that ketamine increases cerebral blood flow, at least in healthy animals and neurologically intact humans. The increases seem to be greatest in the regions which, on reflection, are not surprising: the thalamus, the limbic system, and the frontal cortex. Anterior cingulate blood flow increased by 38% in a study by Långsjö et al (2003).

But what about $CMRO_2$? And, for CICM exam relevance, how does the effect of ketamine on $CMRO_2$ compare to the effect of propofol? The problem with this question is that no study has so far concurrently measured cerebral blood flow, $CMRO_2$ and cerebral glucose metabolism and the findings of studies which address these separately are somewhat confusing. Laaksonen et al (2018) used PET to look at the cerebral metabolic rate for glucose (a good surrogate for oxygen) and found that with propofol glucose metabolism in the brain decreased to 71% of baseline, whereas with ketamine it had remained essentially unchanged. From this, one might assue that ketamine has no effect on $CMRO_2$. However, these were healthy volunteers with relatively low doses. This finding is supported by Långsjö et al (2003), whose PET investigations also concluded that *"there were no statistically significant absolute changes in rCMRO$^2$in any brain region studied"* at subanaesthetic doses in healthy volunteers. Blood flow increased, but those frontal regions did not appear to be using any additional oxygen. The same group nailed this down with their 2005 study, demonstrating that ketamine seemed to uncouple cerebral blood flow from cerebral oxygen consumption. However, at the higher doses used in their second experiment, they were able to detect a statistically significant increase in the oxygen consumption specifically by the frontal cortex, by about 15%.

So where does that leave us? How would you summarise this disagreement of several decades, in a way which maintains an attachment to fact without offending any primitive beliefs? A suggested wording follows:

- Ketamine uncouples cerebral blood flow from cerebral metabolic activity:
    - Ketamine increases global blood flow
    - Ketamine disproportionally increases regional blood flow to the limbic system and frontal lobe
    - At the same time, low dose sub-anaesthetic ketamine has minimal effect on cerebral metabolism of glucose or on $CMRO_2$
    - Anaesthetic doses of ketamine increase the regional $CMRO_2$ of the frontal cortex, but not as much as would be expected from the increase in blood flow.

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## Indications for Use

Kurdi et al (2014) and Pribish et al (2020) have produced some excellent overviews of the contemporary uses for ketamine. Considering the basic science orientation of this section and the fact that other authors have already said it best, only a short list of indications will be offered here, without overmuch elaboration.

**Indications for the use of ketamine:**

- General anaesthesia
- Procedural sedation
- Acute pain analgesia (as opioid sparing co-analgesic)
- Chronic pain analgesia (as management of opioid-related hyperalgesia)
- Antidepressant (for treatment of treatment-resistant depression)
- As a bronchodilator in the management of status asthmaticus
- To prevent postanaesthesia shivering
- As a fourth-line agent in the management of super-refractory status epilepticus

Also, ketamine has several other, weirder powers:

- It exerts an anti-inflammatory effect in septic patients
- It can ameliorate the effects of opioid and alcohol withdrawal

- It inhibits rabies virus replication.

## Contraindications and adverse effects

There are basically no absolute contraindications to the use of ketamine, apart from some sort of genuine ketamine allergy, which is rare enough to get published in case reports. There are, potentially, a few *relative* contraindications:

- **Extremes of hypertension:** you would not want to use an anaesthetic dose of this drug on a patient with a big juicy phaeochromocytoma, for example
- **Procedures which require muscle relaxation:** Ketamine tends to produce an increase in muscle tone, which is great for airway muscles, but quite counterproductive if you are trying to reduce a dislocated hip. So, in these scenarios people occasionally add another general anaesthetic or muscle relaxant, which of course defies logic because it mandates the use of airway support manoeuvres, obliterating the major benefits of using ketamine.
- **Psychosis** generally gets worse if you feed it ketamine, and previously lucid individuals can develop features of psychosis while under the influence of ketamine.
- **Secretions increase**, in particular save, requiring suctioning and potentially producing laryngospasm.

## Interactions

Ketamine is metabolised by multiple CYP450 enzymes and so could potentially interact with inhibitors or activators of these enzymes, but in general major drug interactions are rarely a barrier. Andrade et al (2017), after reviewing the literature on this subject, concluded that at least for subanaesthetic doses there are no major drug interactions affecting the use of ketamine.

## Chronic Toxicity

**Major adverse effects** which are unrelated to its sedative or haemodynamic effects include:

- **Nephrotoxicity and ulcerative cystitis:** Chu et al (2008) dramatically referred to this as *"the destruction of the lower urinary tract"*. Not without cause: papillary necrosis and interstitial fibrosis are the effects of chronic exposure of the urinary tract to ketamine metabolites.
- **Hepatotoxicity** with large doses of ketamine is also occasionally seen in case reports; though very large doses are required (eg. serial courses of 100+ hours of ketamine infusion at 10-20mg/hr)
- **Memory loss and short term memory impairment** is seen with chronic use: particularly spatial memory.

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## Acute Toxicity and Overdose

The acute toxicity of ketamine can be described in terms of the extension of its useful effects. Dissociative anaesthesia becomes coma, analgesia becomes delirium, a pleasant dream trip becomes a catastrophic mind-obliterating ego crisis. The community prevalence of hardcore ketamine abuse is fortunately so low that massive ketamine overdoses are virtually unknown. What becomes apparent from literature searches is that these are generally quite benign. As an example, a two-year-old girl was accidentally given 230mg (20mg/kg) of IM ketamine for a minor surgical procedure, and was back to normal after four hours, only requiring 2L/min of oxygen by nasal prongs (Bowman et al, 2019). Similar cases with up to 50mg/kg of IV ketamine are reported, similarly without major consequences for the patients, apart from the occasional undignified airway manoeuvre. Deaths, of course, are possible. Likata et al (1994) reported a case of fatal intentional poisoning (*"a homicide for homosexual ends"*), which culminated in pulmonary oedema and death. The dose is unknown and the only witness was a suspect whose account of the episode was described as "incomplete", but toxicology analysis suggests that the dose must have been truly titanic: blood levels were 27.4 μg/ml, as compared to peak levels of 1.2–2.4 μg/ml which are usually seen with the induction of anaesthesia.

Previous chapter: Propofol

Next chapter: Midazolam

## References

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